Aryne Chemistry

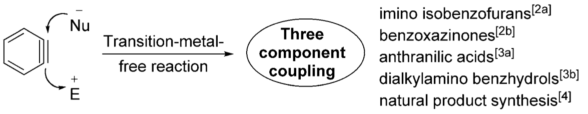
DOI: 10.1002/anie.201106984

Arynes in Transition-Metal-Free Multicomponent Coupling Reactions**

*Sachin Suresh Bhojgude and Akkattu T. Biju**

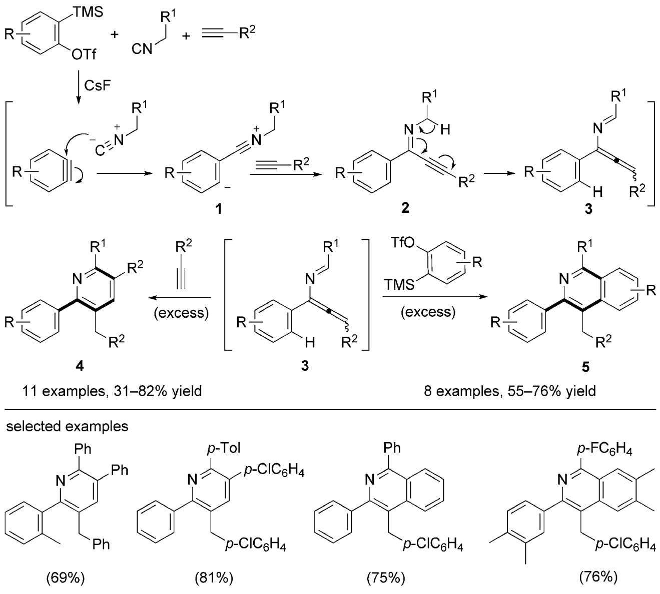
arenes · arynes · isocyanides ·
multicomponent reactions · synthetic methods

Arynes are highly electrophilic reactive intermediates, which have been extensively utilized in various carbon–carbon and carbon–heteroatom bond-forming reactions.[1] Recent developments in aryne chemistry have been devoted to transition-metal-free reactions, which mainly include the initial addition of nucleophiles to arynes and subsequent trapping of the aryl anion intermediate with electrophiles [Eq. (1)]. If the nucleophile and electrophile do not belong to the same molecule, the overall process is a unique three component coupling, in which the aryne is inserted between the other two coupling partners. This versatile transition-metal-free method has been applied to the synthesis of valuable heterocycles including imino isobenzofurans and benzoxazinones,[2] 1,2-disubstituted benzene derivatives including anthranilic acids,[3] and in natural product synthesis.[4] Recently, the groups of Huang,[5] Stoltz,[6] Miyabe,[7] and Yoshida[8] expanded this concept further by developing new multicomponent reactions (MCRs) involving arynes. The key to the success of these reactions is the fluoride-induced mild reaction conditions for the generation of arynes from 2-(trimethylsilyl)aryl triflates.[9]



(1)

Sha and Huang demonstrated a multicomponent reaction of arynes, isocyanides, and terminal alkynes, which provided direct access to polysubstituted pyridines and isoquinolines with excellent selectivity.[5] It is noteworthy that the assembly of four molecules took place in a highly efficient and atom-economic manner. The key to success for the observed selectivity arose from the appropriate reaction conditions: with an excess of terminal alkynes, pyridines **4** were formed and with an excess of arynes, isoquinolines **5** were formed (Scheme 1). The reaction proceeds with the formation of 1,3-zwitterionic intermediate **1** from an aryne and an isocyanide; this intermediate is intercepted by the terminal alkyne to generate the imine intermediate **2**, which undergoes a 1,5-hydride shift to generate the allenyl imine intermediate **3**. The successive cycloaddition of **3** with another molecule of the terminal alkyne or aryne afforded either **4** or **5**.



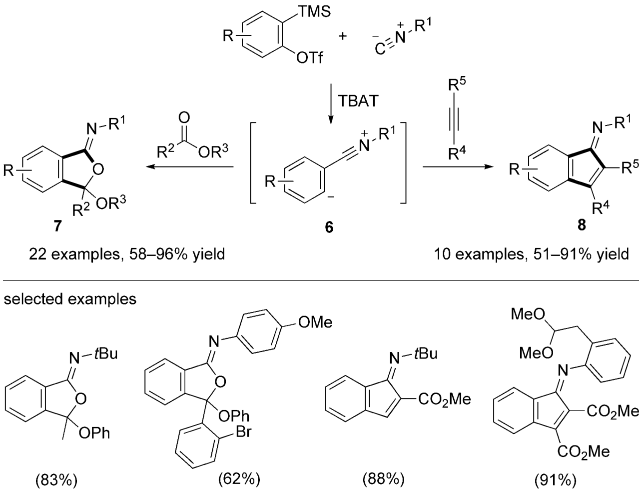
Scheme 1. Multicomponent coupling of arynes, isocyanides, and terminal alkynes.[5] Tf = trifluoromethanesulfonyl, TMS = trimethylsilyl, *p*-Tol = *p*-tolyl.

In their quest to develop an aryne-intercepted version of the Passerini reaction, Stoltz and co-workers uncovered a novel three-component reaction of arynes, isocyanides, and phenyl esters that provided the phenoxy iminoisobenzofuran **7** in good yield (Scheme 2).[6] Wide substrate scope, mild reaction conditions, and the formation of an unusual heterocyclic scaffold are the noteworthy features of this reaction. Acidic hydrolysis of **7** afforded *o*-ketobenzamides. It is important to note that the combination of this MCR and subsequent hydrolysis can be carried out in a single sequence, thus leading to a one-pot synthesis of *o*-ketobenzamides.

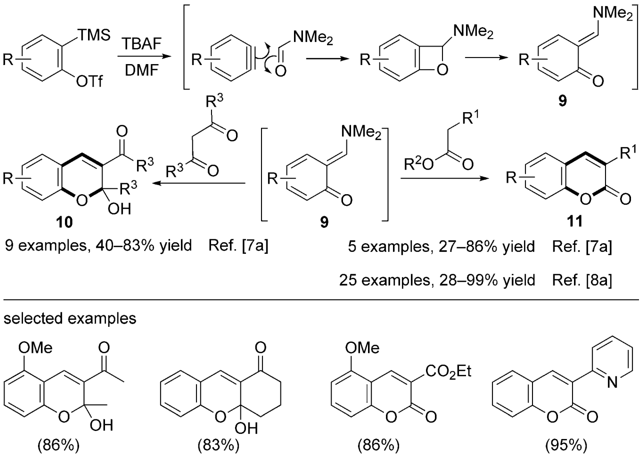
---

[*] S. S. Bhojgude, Dr. A. T. Biju
Organic Chemistry Division
CSIR-National Chemical Laboratory (CSIR-NCL)
Dr. Homi Bhabha Road, Pune-411008 (India)
E-mail: at.biju@ncl.res.in

[**] Generous financial support from CSIR-NCL in the form of a start-up grant for a new faculty is kindly acknowledged. S.S.B. would like to thank CSIR-New Delhi for the award of Junior Research Fellowship. We also thank Anup Bhunia for helpful discussions.



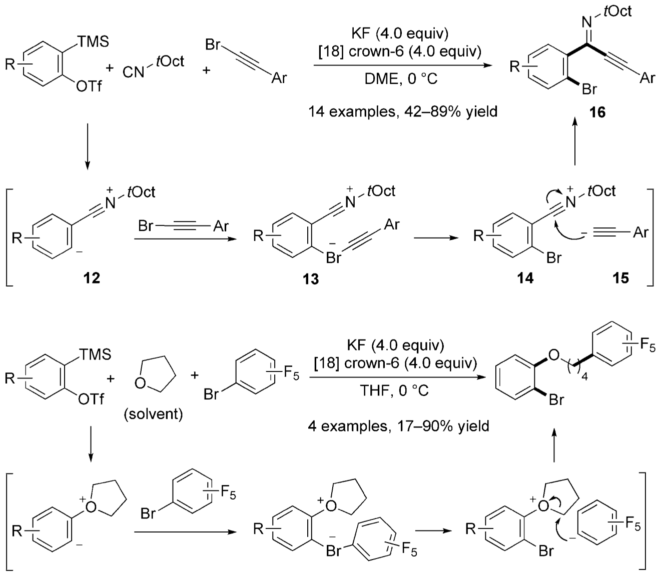
Scheme 2. Multicomponent coupling of arynes and isocyanides with either phenyl esters or electrophilic alkynes.[6] TBAT = tetra-*N*-butylammonium difluorotriphenylsilicate.



Scheme 3. Multicomponent coupling of arynes and DMF with active methylene compounds.[7a,8a] TBAF = tetra-*n*-butylammonium fluoride.

When the ester component of this MCR was replaced by an electron-deficient alkyne, the reaction afforded carbocyclic imino indenones **8**. The imino indenone formation took place with internal and terminal alkynes. The selective addition of isocyanides to arynes in the presence of electrophilic alkynes is worthy of note.[10] Although a stepwise mechanism for the product formation is proposed, it is conceivable that the 1,3-zwitterionic intermediate **6**, generated from an aryne and an isocyanide, undergoes a [3+2] cycloaddition with the third component, thus leading to the expected product formation.

Recently, the research groups of Miyabe[7a] and Yoshida[8a] independently disclosed a three-component coupling reaction involving aryne, dimethyl formamide (DMF), and an active methylene compound. The underlying principle is the generation of *o*-quinone methides **9** by the 1:1 reaction of an aryne and DMF, which proceeds with the insertion of the carbonyl group of DMF into the aryne (Scheme 3). In the presence of cyclic or acyclic 1,3-diketones as the third component, the reaction afforded 2*H*-chromenes **10**, and coumarine derivatives **11** were formed when β-ketoester or α-(hetero)aryl esters were used as the third component (Scheme 3). Intriguingly, in this process, many selectivity issues arose and the formation of the undesired insertion products were suppressed.[11]



Scheme 4. Multicomponent coupling of arynes and isocyanides (or cyclic ethers) with alkynyl (or polyfluoroaryl) bromides.[8b] DME = 1,2-dimethoxyethane, THF = tetrahydrofuran.

In the context of their continued interest in aryne chemistry, the Yoshida group, very recently, incorporated alkynyl (polyfluorinated aryl) bromides as the third component in an aryne reaction.[8b] Following the tentative mechanism shown in Scheme 4, the 1,3-zwitterionic intermediate **12** generated from an isocyanide and an aryne reacts with alkynyl bromides, thus resulting in the formation of the aryl–bromide bond in **14** and aryl acetylide **15** via the bromine ate complex **13**. Subsequent C−C bond-formation afforded *o*-functionalized bromoarenes **16** with the formation of two C−C bonds and a C−Br bond (Scheme 4). Interestingly, cyclic ethers can also be used as the nucleophilic trigger to generate the 1,4-dipole, which can be intercepted with polyfluoroaryl or alkynyl bromides with good functional group compatibility. In addition, the synthetic potential of the present method was demonstrated in the total synthesis of a benzo[*b*]oxepine-based nonsteroidal estrogen.

In conclusion, the groups of Huang, Stoltz, Miyabe, and Yoshida have described new avenues for the transition-metal-free multicomponent coupling involving arynes to afford valuable heterocycles and 1,2-disubstituted arenes. Further developments in this area will provide a deeper understanding of the mechanism and the utility of other coupling partners in this transformation. It is reasonable to assume that the rapid and one-pot construction of molecular complexity using aryne reactions will soon find more applications in complex natural product synthesis.[4]

Received: October 3, 2011

[1] For reviews, see a) H. H. Wenk, M. Winkler, W. Sander, *Angew. Chem.* **2003**, *115*, 518; *Angew. Chem. Int. Ed.* **2003**, *42*, 502; b) H. Pellissier, M. Santelli, *Tetrahedron* **2003**, *59*, 701; for a Highlight, see c) D. Peña, D. Pérez, E. Guitián, *Angew. Chem.* **2006**, *118*, 3659; *Angew. Chem. Int. Ed.* **2006**, *45*, 3579, and references therein.

[2] For selected examples, see a) H. Yoshida, H. Fukushima, J. Ohshita, A. Kunai, *Angew. Chem.* **2004**, *116*, 4025; *Angew. Chem. Int. Ed.* **2004**, *43*, 3935; b) H. Yoshida, H. Fukushima, J. Ohshita, A. Kunai, *J. Am. Chem. Soc.* **2006**, *128*, 11040; c) M. Jeganmohan, C.-H. Cheng, *Chem. Commun.* **2006**, 2454.

[3] For selected examples, see a) H. Yoshida, T. Morishita, J. Ohshita, *Org. Lett.* **2008**, *10*, 3845; b) H. Yoshida, T. Morishita, H. Fukushima, J. Ohshita, A. Kunai, *Org. Lett.* **2007**, *9*, 3367.

[4] a) D. Soorukram, T. Qu, A. G. M. Barrett, *Org. Lett.* **2008**, *10*, 3833; b) I. Larrosa, M. I. Da Silva, P. M. Gómez, P. Hannen, E. Ko, S. R. Lenger, S. R. Linke, A. J. P. White, D. Wilton, A. G. M. Barrett, *J. Am. Chem. Soc.* **2006**, *128*, 14042.

[5] F. Sha, X. Huang, *Angew. Chem.* **2009**, *121*, 3510; *Angew. Chem. Int. Ed.* **2009**, *48*, 3458.

[6] K. M. Allan, C. D. Gilmore, B. M. Stoltz, *Angew. Chem.* **2011**, *123*, 4580; *Angew. Chem. Int. Ed.* **2011**, *50*, 4488.

[7] a) E. Yoshioka, S. Kohtani, H. Miyabe, *Angew. Chem.* **2011**, *123*, 6768; *Angew. Chem. Int. Ed.* **2011**, *50*, 6638; for a related report, see: b) E. Yoshioka, S. Kohtani, H. Miyabe, *Org. Lett.* **2010**, *12*, 1956.

[8] a) H. Yoshida, Y. Ito, J. Ohshita, *Chem. Commun.* **2011**, *47*, 8512; b) H. Yoshida, Y. Asatsu, Y. Mimura, Y. Ito, J. Ohshita, K. Takaki, *Angew. Chem.* **2011**, *123*, 9850; *Angew. Chem. Int. Ed.* **2011**, *50*, 9676.

[9] a) Y. Himeshima, T. Sonoda, H. Kobayashi, *Chem. Lett.* **1983**, 1211; for a modified procedure, see b) D. Peña, A. Cobas, D. Pérez, E. Guitián, *Synthesis* **2002**, 1454.

[10] For an account of the addition of isocyanides to electrophilic alkynes and related chemistry, see V. Nair, C. Rajesh, A. U. Vinod, S. Bindu, A. R. Sreekanth, J. S. Mathen, L. Balagopal, *Acc. Chem. Res.* **2003**, *36*, 899.

[11] For selected examples, see a) U. K. Tambar, B. M. Stoltz, *J. Am. Chem. Soc.* **2005**, *127*, 5340; b) H. Yoshida, M. Watanabe, J. Ohshita, A. Kunai, *Chem. Commun.* **2005**, 3292; c) H. Yoshida, M. Watanabe, J. Ohshita, A. Kunai, *Tetrahedron Lett.* **2005**, *46*, 6729.